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Chapter 70: Schizophrenia

INTRODUCTION

- *Schizophrenia* is a chronic illness with positive symptoms (delusions, hallucinations), negative symptoms (anhedonia, social isolation), and cognitive dysfunction (impaired working memory, executive function), leading to impaired psychosocial functioning.

CLINICAL PRESENTATION

- Symptoms may include positive symptoms such as hallucinations, delusions, ideas of influence, disconnected thoughts, illogical conversation, and ambivalence; negative symptoms such as alogia, avolition, flat affect, anhedonia, and social isolation; and cognitive dysfunction such as impaired attention, working memory, and executive function. Accompanying issues may include uncooperativeness, hostility, aggression, impaired self-care, and disturbed sleep and appetite.
- After the acute psychotic episode resolves, residual features may include anxiety, suspiciousness, lack of motivation, poor insight, impaired judgment, social withdrawal, difficulty learning from experience, and poor self-care skills.
- Comorbid psychiatric and medical disorders, such as depression, anxiety, substance use, respiratory, cardiovascular, and metabolic conditions, can occur. Medication nonadherence is common too.

DIAGNOSIS

- The *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed., text revision (*DSM-5-TR*) includes the following key points for diagnosis:

  ✓ Two or more positive, negative, or cognitive symptoms must be present for a significant portion of time during a one-month period, and at least one of these must be delusions, hallucinations, or disorganized speech.

- Before treatment, perform a mental status and neurologic examination, a physical examination (vitals including height and weight), complete family and social history, psychiatric diagnostic interview, and laboratory workup (complete blood count [CBC], electrolytes, hepatic function, renal function, electrocardiogram [ECG], fasting serum glucose, serum lipids, thyroid function, and urine toxicology screen).

TREATMENT

- Goals of Treatment: The goals are to alleviate target symptoms, avoid medication side effects, improve psychosocial functioning and productivity, ensure compliance with the regimen, and prevent relapse. Involve the patient in treatment planning.

NONPHARMACOLOGIC THERAPY

- Psychosocial rehabilitation to improve adaptive functioning is key in nonpharmacologic schizophrenia therapy. Family-involved programs for supportive employment and housing are "best practices," reducing rehospitalization and improving community functioning.
- The recovery-based, patient-centered care approach focuses on lifetime aspirations and goals rather than just symptom reduction.

PHARMACOLOGIC THERAPY

- Both first-generation (FGAs) and second-generation antipsychotics (SGAs) treat schizophrenia. The FDA-approved XT (**xanomeline and**

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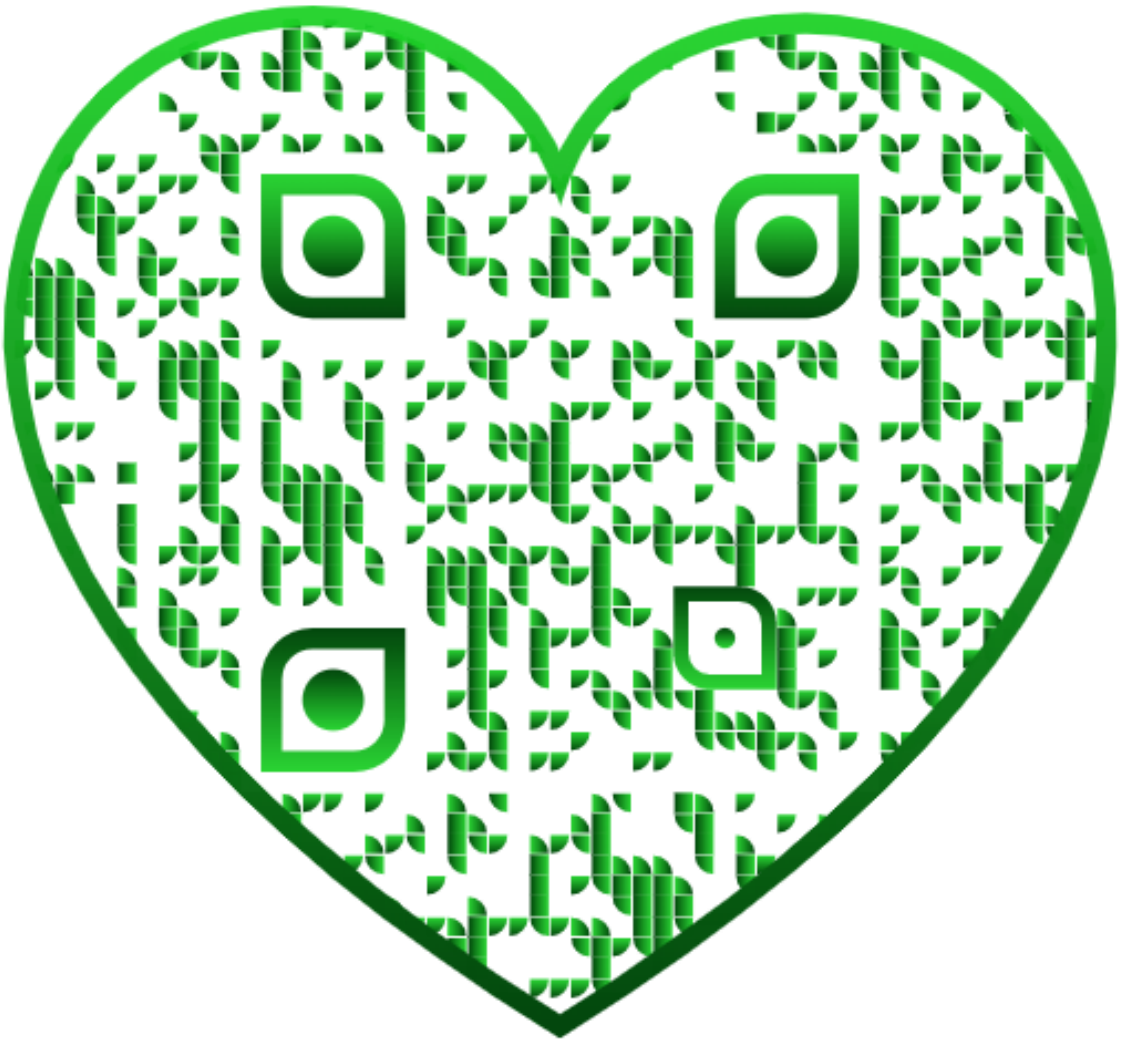

trospium) is the first schizophrenia treatment not directly modulating dopamine receptors. Available antipsychotics and dosage ranges are shown in **Table 70-1**.

- **Table 70-2** summarizes the long-acting injectable antipsychotics (LAIAs), including dosage range, conversion from oral to LAIA, and injection method/technique.
- The exact antipsychotic mechanism is unknown. FGAs have high D_2, low serotonin-2 receptor (5-HT) antagonism. SGAs show moderate-high D_2 and high 5-HT_{2A} antagonism. **Clozapine** has low D_2 and high 5-HT_{2A} antagonism.
- Select antipsychotics based on: (1) avoiding adverse effects, (2) concurrent medical or psychiatric conditions, and (3) patient or family response history. **Figure 70-1** shows an algorithm for schizophrenia management. Clozapine has superior efficacy for suicidal behavior.
- For first-episode schizophrenia, start dosing at the lower range. SGAs offer better treatment retention and relapse prevention than FGAs. **Aripiprazole, risperidone,** or **ziprasidone** may be preferred first line.
- Risperidone injection is more effective than oral risperidone in preventing relapse over one year for first-episode schizophrenia. Consider long-acting antipsychotics in stages 1A, 1B, and 2 for reduced hospitalizations and relapse prevention.
- XT monotherapy can also be used in stage 2.
- In stage 3, clozapine monotherapy is recommended.
- Stage 4, it is for patients with inadequate response to clozapine. However, minimal evidence exists for treatment options at this point. Antipsychotic combinations are controversial and have limited support for increased efficacy.
- Response predictors include previous response, no substance use, acute, short illness, later onset, affective symptoms, family history, adherence, employment, and good premorbid function. Negative symptoms respond less to treatment.
- An initial dysphoric response (eg, dislike of the medication or feeling worse, combined with anxiety or akathisia) signals poor outcomes, side effects, and nonadherence.
- A strong therapeutic alliance between patient and clinician is crucial.
- **Table 70-3** lists incidence rates for common antipsychotic adverse effects, often related to binding affinities.
- Anticholinergic effects, such as impaired memory, dry mouth, constipation, tachycardia, blurred vision, inhibition of ejaculation, and urinary retention, are most common with low-potency FGAs, clozapine, and olanzapine; older patients are more sensitive.
- Taking most or all of the antipsychotic dose at bedtime can reduce sedation.
- Antipsychotics are lipophilic, bind to membranes and proteins, have large distribution volumes, and are mostly metabolized by cytochrome P450 (CYP) pathways, with pharmacogenetics affecting pharmacokinetics (**Table 70-1**).
- Most antipsychotics, except quetiapine and ziprasidone, have half-lives ≥24 hours and can be dosed once daily.
- Antipsychotic pharmacokinetics are affected by enzyme inducers/inhibitors. Smoking may increase clearance by up to 50%. **Asenapine,** a CYP2D6 inhibitor, affects other medications. **Fluvoxamine**, a CYP1A2 inhibitor, increases clozapine levels two- to threefold. **Ketoconazole** notably reduces **lurasidone** metabolism; avoid use together. **Carbamazepine** lowers aripiprazole levels. Reduce **iloperidone** dose by 50% with CYP2D6 inhibitors such as **fluoxetine** or **paroxetine**.

FIGURE 70-1

Suggested pharmacotherapy algorithm for treatment of schizophrenia.

Schizophrenia should be treated in the context of an interprofessional model that addresses the psychosocial needs of the patient, necessary

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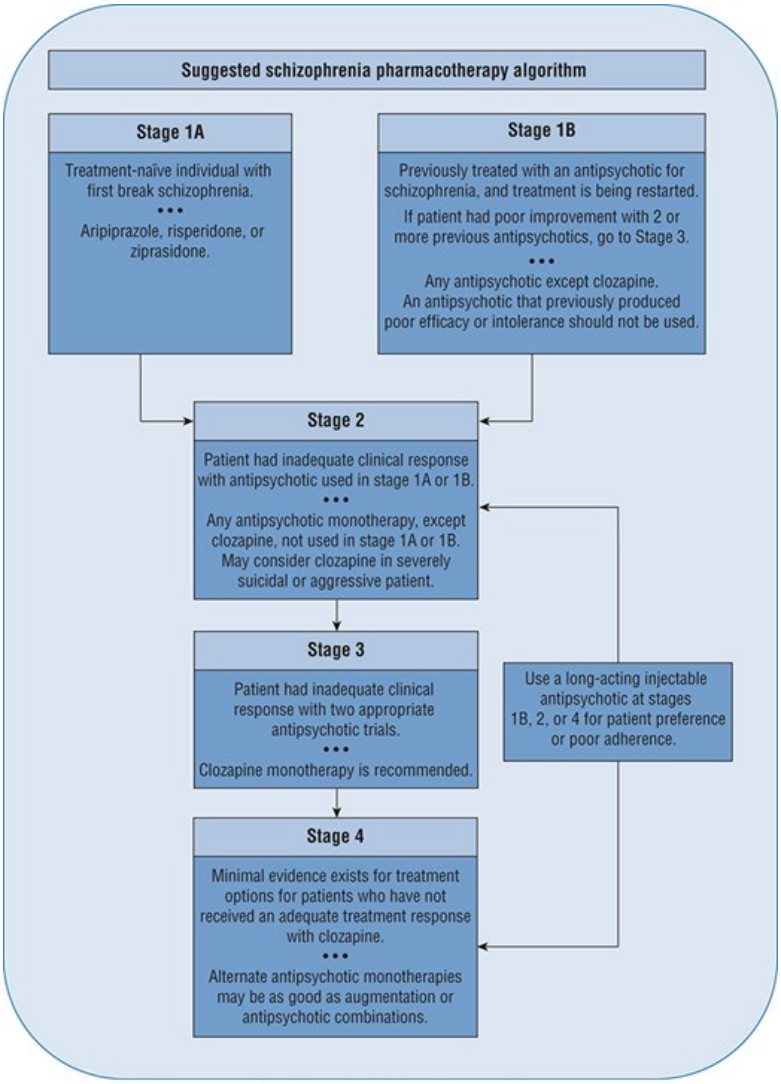
psychiatric pharmacotherapy, psychiatric co-occurring mental disorders, treatment adherence, and any medical problems the patient may have.


Suggested schizophrenia pharmacotherapy algorithm
Stage 1A
Treatment-naïve individual with first break schizophrenia.
• • •
Aripiprazole, risperidone, or ziprasidone.
Stage 1B
Previously treated with an antipsychotic for schizophrenia, and treatment is being restarted.
If patient had poor improvement with 2 or more previous antipsychotics, go to Stage 3.
• • •
Any antipsychotic except clozapine.
An antipsychotic that previously produced poor efficacy or intolerance should not be used.
Stage 2
Patient had inadequate clinical response with antipsychotic used in stage 1A or 1B.
• • •
Any antipsychotic monotherapy, except clozapine, not used in stage 1A or 1B.
May consider clozapine in severely suicidal or aggressive patient.
Stage 3
Patient had inadequate clinical response with two appropriate antipsychotic trials.
• • •
Clozapine monotherapy is recommended.
Use a long-acting injectable antipsychotic at stages 1B, 2, or 4 for patient preference or poor adherence.
Stage 4
Minimal evidence exists for treatment options for patients who have not received an adequate treatment response with clozapine.
• • •
Alternate antipsychotic monotherapies may be as good as augmentation or antipsychotic combinations.

Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Lisa M. Holle, Cecily V. DiPiro: *DiPiro's Pharmacotherapy Handbook, 13th Edition*
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TABLE 70-1

Available Antipsychotics, Dosage Ranges, and Major Metabolic Pathways

Generic Name	Starting Dose (mg/day)	Usual Dosage Range (mg/day)	Comments	Major Metabolic Pathways
First-Generation Antipsychotics				
Chlorpromazine	25–150	200–800	Most weight gain among FGAs	FMO3, CYP3A4
Fluphenazine	2.5–10	5–20		
Haloperidol	1–5	5–20	Higher dropout rate in first episode	**CYP2D6**, CYP1A2, CYP3A4

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Loxapine	20	60–100		
Loxapine inhaled	10	10	Maximum 10 mg per 24 hours; REMS program	
Perphenazine	8–16	8–64		**CYP2D6**
Thiothixene	6–10	15–30		
Trifluoperazine	4–10	15–30		
Second-Generation Antipsychotics				
Aripiprazole	5–15	10–30		**CYP2D6, CYP3A4**
Asenapine	5	10–20	Sublingual only, no food or drink for 10 minutes after administration	**CYP1A2, UGT1A4**, CYP2D6, CYP3A4
Brexpiprazole	1	2–4		**CYP2D6, CYP3A4**
Cariprazine	1.5	1.5–6	Due to long half-life, steady state is not reached for several weeks	**CYP3A4**, CYP2D6
Clozapine	12.5–25	300–600	Check plasma level before exceeding 600 mg	**CYP1A2, CYPD6, CYP3A4**
Iloperidone	2	12–24	Care with dosing in CYP2D6 slow metabolizers	**CYP2D6, CYP3A4**
Lumateperone	42	42	Bioavailability increased by 9% with high-fat meal	**CYP3A4**, CYP1A2, CYP2C8, Aldoketoreductase 1C1, UGT1A1, UGT1A4, UGT 2B15
Lurasidone	40	40–120	Take with food, ≥350 calories (1460 J)	**CYP3A4**, CYP1A2
Olanzapine	5–10	10–20	Avoid in first episode because of weight gain	CYP1A2, CYP3A4, FMO3
Paliperidone	3–6	3–12	Bioavailability increased when administered with food	Renal unchanged (59%) CYP3A4 and multiple pathways
Quetiapine	50	400–800		**CYP3A4,** CYP3A5
Quetiapine XR	300	400–800		**CYP3A4,** CYP3A5
Risperidone	2	2–6		**CYP2D6**, CYP3A4
Ziprasidone	40	80–160	Take with food, ≥500 calories (2100 J)	Aldehyde oxidase, CYP3A4, CYP1A2
Nondopaminergic Medications				
Xanomeline and trospium chloride	100/40	200/40–250/60	Give in two divided doses daily at least 1 hour before or 2 hours after a meal. Contraindicated in patients with urinary/gastric retention	**CYP2D6**, CYP2B6, CYP1A2, CYP2C9, CYP2C19

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Note: In first-episode patients, starting dose and target dose should generally be 50% of the usual dose range.

TABLE 70-2

Summary of Available Long-Acting Injectable Antipsychotics (LAIAs)

Aripiprazole Monohydrate (Abilify Maintena)			
Dose range: 300–400 mg	Max dose: 400 mg Q month	Dosing frequency: Monthly	Oral overlap: 14 days
Dose conversion: 400 mg/month (consider lower dose for CYP 2D6/3A4 PM)			
Tpeak: 4–7 days (D) 5–7 days (G)	Half-life: 300 mg: 30 days 400 mg: 47 days (G)	Tss: By 4th dose	Injection site: D, G
Comments: Give no sooner than 26 days between injections; major CYP2D6 & CYP3A4 substrate			
Aripiprazole Monohydrate (Abilify Asimtufii)			
Dose range: 720–960 mg	Max dose: 960 mg	Dosing frequency: Every 2 months	Oral overlap: 14 days (10–20 mg PO)
Dose conversion: 960 mg every 2 months (consider lower dose for CYP 2D6/3A4 PM)			
Tpeak: 1–49 days	Half-life: Not reported	Tss: Not reported	Injection site: G
Comments: Avoid in those who are both a CYP2D6 & CYP3A4 PM or CYP3A4 inducers			
Aripiprazole Lauroxil (Aristada)			
Dose range: 441–1064 mg	Max dose: 882 mg Q month	Dosing frequency: Monthly: 441, 662, 882 mg Every 6 weeks: 882 mg Every 2 months: 1064 mg	Oral overlap: 3 weeks if not given with Aristada Initio
Dose conversion: 10 mg/day PO: 441 mg IM/month; 15 mg/day PO: 662 mg IM/month, or 882 mg IM every 6 weeks, or 1064 mg every 2 months; 20 mg/day or more: 882 mg IM/month			
Tpeak: Not available	Half-life: 54–57 days	Tss: 4 months	Injection site: D, G
Comments: CYP2D6 and CYP3A4 major substrate			
Aripiprazole Lauroxil Extended-Release (Aristada Initio)			
Dose range: 675 mg	Max dose: 675 mg	Dosing frequency: Single dose to initiate or reinitiate Aristada lauroxil. Not for repeat dosing.	Oral overlap: Administer with one 30-mg dose or PO aripiprazole if not at PO Tss
Dose conversion: Not applicable			
Tpeak: 16–35 days	Half-life: 15–18 days	Tss: Not applicable	Injection site: D, G

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(median: 27 days)			
Comments: CYP2D6 and CYP3A4 substrate			
Fluphenazine Decanoate			
Dose range: 6.25–100 mg	Max dose: 100 mg	Dosing frequency: 2–4 weeks	Oral overlap: Decrease PO dose by half after 1st inj., then stop with 2nd inj.
Dose conversion: For each 10 mg/day PO, give 12.5 mg IM every 3 weeks			
Tpeak: 8–10 hours	Half-life: 6–9 days for single inj.; 14–26 days for multiple injections	Tss: 2 months	Injection site: D, G (Z-track technique)
Comments: Monitor for hypotension. In sesame oil.			
Haloperidol Decanoate			
Dose range: 50–450 mg	Max dose: 450 mg	Dosing frequency: Monthly	Oral overlap: Taper and discontinue PO after 2–3 injections
Dose conversion: For each 5 mg/day PO, give 50–75 mg every 4 weeks; split 1st inj. by 3–7 days if initial dose >100 mg			
Tpeak: 6 days	Half-life: 21 days	Tss: 3–4 months	Injection site: D, G (Z-track technique)
Comments: Do not administer more than 3 mL per injection site. In sesame oil.			
Olanzapine Pamoate (Zyprexa Relprevv)			
Dose range: 150–405 mg	Max dose: 300 mg every 2 weeks or 405 mg every month	Dosing frequency: 2–4 weeks	Oral overlap: None
Dose conversion: 10 mg/day PO: 210 mg every 2 weeks × 4 doses or 405 mg every 5 weeks; 15 mg/day PO: 300 mg every 2 weeks for 4 doses; 20 mg PO/day: 300 mg every 2 weeks			
Tpeak: 7 days	Half-life: 30 days	Tss: 3 months	Injection site: G
Comments: Requires REMS. Observe patient for at least 3 hours post injection due to risk of post injection delirium. Do not massage muscle after inj.			
Paliperidone Palmitate (Erzofri)			
Dose range: 39–351 mg	Max dose: 351 mg	Dosing frequency: Single 351-mg dose to initiate or reinitiate. Monthly doses thereafter.	Oral overlap: None
Dose conversion: 3 mg/day PO: 39–78 mg; 6 mg/day PO: 117 mg; 9 mg/day PO: 156 mg; 12 mg/day PO: 234 mg			
Tpeak: 16–28 days	Half-life: 27 days	Tss: 4 months	Injection site: D, G; 351-mg dose must be given in deltoid
Comments: Erzofri does not require two separate loading injections one-week apart to avoid oral overlap (unlike Invega Sustenna). Monthly injections start following a single initiation dose of 351 mg. The follow-up dose range, dosing frequency, and renal dosage adjustments are the same as Invega Sustenna.			

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Paliperidone Palmitate (Invega Sustenna) (1MPP)			
Dose range: 39–234 mg	Max dose: 234 mg Q month	Dosing frequency: Monthly	Oral overlap: None following two loading doses (234 mg and 156 mg) given one week apart
Dose conversion: 3 mg/day PO: 39–78 mg; 6 mg/day PO: 117 mg; 9 mg/day PO: 156 mg; 12 mg/day PO: 234 mg			
Tpeak: 13 days	Half-life: 25–49 days	Tss: 2–3 months	Injection site: D, G; loading doses must be given in deltoid
Comments: CrCl 50–79 mL/min (0.83–1.32 mL/s) initiate 156 mg on day 1 and 117 mg 1 week later. Avoid if CrCl <50 mL/min (0.83 mL/s). P-glycoprotein substrate.			
Paliperidone Palmitate (Invega Trinza) (3MPP)			
Dose range: 274–819 mg	Max dose: 819 mg every 3 months	Dosing frequency: 3 months	Oral overlap: Not applicable
Dose conversion: Convert from 1MPP: 78 mg: 273 mg; 117 mg: 410 mg; 156 mg: 546 mg; 234 mg: 819 mg			
Tpeak: 30–33 days	Half-life: 84–95 days (D); 118–139 days (G)	Tss: Not applicable	Injection site: D, G
Comments: Requires at least 4-month trial with 1MPP. Avoid in patients with CrCl <50 mL/min (0.83 mL/s).			
Paliperidone Palmitate (Invega Hafyera) (6MPP)			
Dose range: 1092–1560 mg	Max dose: 1560 mg every 6 months	Dosing frequency: 6 months	Oral overlap: Not applicable
Dose conversion: Convert from 1MPP: 156 mg: 1092 mg; 234 mg: 1560 mg			
Convert from 3MPP: 546 mg: 1092 mg; 819 mg: 1560 mg			
Tpeak: 29–32 days	Half-life: 148–159 days	Tss: Not applicable	Injection site: G
Comments: Requires at least 4-month trial with 1MPP or 1 cycle of 3MPP. Avoid in patients with CrCl <50 mL/min (0.83 mL/s)			
Risperidone (Risperdal Consta)			
Dose range: 12.5–50 mg	Max dose: 50 mg every 2 weeks	Dosing frequency: 2 weeks	Oral overlap: 21 days after initial injection
Dose conversion: ≤3 mg/day PO: 25 mg IM/2 weeks; >3 to ≤5 mg/day PO: 37.5 mg IM/2 weeks; >5 mg/day PO: 50 mg IM/2 weeks			
Tpeak: 29–31 days	Half-life: 3–6 days	Tss: 2 months	Injection site: D, G
Comments: Requires refrigeration. Do not increase dose more frequently than every 4 weeks			
Risperidone (Uzedy)			

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Dose range: 50–150 mg	Max dose: 125 mg Q month or 250 mg every 2 months	Dosing frequency: Monthly	Oral overlap: None
Dose conversion: 2 mg/day PO: 50 mg IM/month or 100 mg IM every 2 months; 3 mg/day PO: 75 mg IM/month or 150 mg IM every 2 months			
Tpeak: Immediately then again in 10–14 days	Half-life: 14–22 days	Tss: 2–3 months	Injection site: Abdomen or upper arm
Comments: Initiate at 50 mg IM every month in renal/hepatic impairment after establishing PO tolerability			
Risperidone (Risvan)			
Dose range: 75–100 mg	Max dose: 100 mg Q month	Dosing frequency: Monthly	Oral overlap: None
Dose conversion: 3 mg/day PO: 75 mg IM/month; 4 mg/day PO: 100 mg IM/month			
Tpeak: 24–48 hours then again in 18–25 days	Half-life: 4–9 days	Tss: 1 month	Injection site: D, G
Comments: Initiate 1 day after the last dose of oral therapy			
Risperidone (Rykindo)			
Dose range: 25–50 mg	Max dose: 50 mg every 2 weeks	Dosing frequency: 2 weeks	Oral overlap: 1 week
Dose conversion: 25 mg IM every 2 weeks; can increase to 37.5–50 mg IM every 2 weeks			
Tpeak: 14–17 days	Half-life: 3–6 days	Tss: 2–4 weeks	Injection site: G
Comments: Requires refrigeration. Do not increase dose more frequently than every 4 weeks			

D, deltoid; DC, discontinue; G, gluteal; Inj., injection; PO, oral; PM, poor metabolizer; Q, every; Tpeak, time to peak; Tss, time to steady-state.

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TABLE 70-3

Relative Incidence of Adverse Medication Effects from Commonly Used Antipsychotics[a,b]

	Sedation	EPS	Anticholinergic	Orthostasis	Weight Gain	Prolactin
Aripiprazole	+	+[c]	+	+	+	±
Asenapine	++	+/++	+	+	++	+
Brexpiprazole	+	+	±	+	+	+
Cariprazine	±	+/++[c]	+	+	+	+
Chlorpromazine	+++	+++	++++	++++	++	++
Clozapine	++++	±	++++	++++	++++	±
Fluphenazine	+	++++	+	+	+	+++
Haloperidol	++	++++	+	+	+	+++
Iloperidone	+	±	+++	+++	+++	+
Lumateperone	+	±	+	+	+	+
Lurasidone	++	+/++[c]	+	+	+	++
Olanzapine	++	++	+++	++	++++	+
Paliperidone	+	++	+	+	++	++++
Perphenazine	+	++++	+	+	+	+++
Quetiapine	+++	+	++++	++	+++	+
Risperidone	++	++	+	++	++	++++
Thiothixene	++	++++	+	+	+	+++
Ziprasidone	++	++	+	+	+	+

[a]Adverse effects shown are relative risk based on doses within the recommended therapeutic range.

[b]Individual patient risk varies depending on patient-specific factors.

[c]Primarily akathisia.

EPS, extrapyramidal side effects—include dystonias, pseudoparkinsonism, akathisia, and tardive dyskinesia.

Relative adverse effect risk: ±, negligible; +, low; ++, moderate; +++, moderately high; ++++, high.

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INITIAL THERAPY

- In the first 7 days, aim to reduce agitation, hostility, anxiety, aggression, and normalize sleep and eating.
- Titrate the antipsychotic to a mid-range effective dose (**Table 70-1**). Start at half the dose for first episode of psychosis compared to chronic cases. Avoid rapid titration. If no improvement occurs in 2 weeks at a therapeutic dose, proceed to the next treatment stage (**Fig. 70-1**).
- For partial responders tolerating their antipsychotic, consider increasing the dose above usual for 2–4 weeks with close monitoring.
- Intramuscular (IM) antipsychotic administration (eg, aripiprazole 5.25–9.75 mg, ziprasidone 10–20 mg, olanzapine 2.5–10 mg, or **haloperidol** 2–5 mg) can treat agitation but don't improve response or reduce hospitalization length. IM **lorazepam,** 2 mg as needed, is a viable alternative, but avoid combining with olanzapine or clozapine due to risks of hypotension and CNS and respiratory depression.
- Inhaled **loxapine** powder is FDA-approved for acute agitation. It is used only in healthcare settings with Risk Evaluation and Mitigation Strategy (REMS) oversight and limited to one 10-mg dose per 24 hours. Patients with bronchospasm-related lung diseases are excluded. It may not be superior to IM or oral alternatives.

STABILIZATION THERAPY

- In weeks 2–3, focus on improving socialization, self-care, and mood. Continue dose titration every 1–2 weeks if no adverse effects occur.
- If an adequate response is seen at a specific dose, maintain it while symptoms improve. Thought disorder improvement may take an additional 6–8 weeks.

MAINTENANCE THERAPY

- The goal of maintenance therapy is relapse prevention. Continue medication for at least 12 months after the first episode's remission. Many experts recommend at least 5 years of treatment. Lifetime pharmacotherapy at the lowest effective dose is necessary in most patients with schizophrenia.
- When switching antipsychotics, taper the first over 1–2 weeks while gradually increasing the second. Slow titration, particularly of FGAs and clozapine, helps prevent cholinergic rebound.
- Relapse studies are unavailable for XT.

MANAGEMENT OF TREATMENT-RESISTANT SCHIZOPHRENIA

- Clozapine is superior to other antipsychotics, with about 60% of patients improving within 6 months.
- Titrate clozapine slowly to reduce orthostatic hypotension. Start with a 12.5-mg test dose, then 25 mg at bedtime if tolerated, increasing every 3 days by 25–50 mg/day up to at least 300 mg/day.
- A 12-hour postdose clozapine serum concentration of at least 350 ng/mL (1.07 µmol/L) indicates efficacy. Monitor serum levels before exceeding 600 mg/day, in cases of severe adverse effects, interactions, changes due to age/pathophysiology, or suspected nonadherence.
- Mood stabilizers like **lithium**, **valproic acid**, and **carbamazepine** may help with labile affect and agitation in refractory schizophrenia. **Selective serotonin reuptake inhibitors** (SSRIs) can address obsessive-compulsive symptoms during clozapine treatment.
- Data on combining antipsychotics is limited, but it is common. If no improvement occurs in 6–12 weeks, one medication should be discontinued. No evidence exists regarding the combination of XT with another antipsychotic.

EXTRAPYRAMIDAL SIDE EFFECTS

Dystonias

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- Dystonias are prolonged muscle contractions, often occurring 24–96 hours after starting or increasing dosage. They can be life-threatening, with examples like pharyngeal–laryngeal dystonias. Other types include trismus, glossospasm, tongue protrusion, blepharospasm, oculogyric crisis, torticollis, and retrocollis. Risk factors include younger males and the use of FGAs, high-potency agents, and high doses.
- Treatment includes IM or IV anticholinergics (**Table 70-4**) or benzodiazepines. Options include **benztropine** 2 mg, **diphenhydramine** 50 mg, **diazepam** 5–10 mg, or **lorazepam** 1–2 mg, with relief in 15–20 minutes (IM) or 5 minutes (IV).
- Prophylactic anticholinergics are advisable with high-potency FGAs in young males or those with prior dystonia. Using lower initial doses or SGAs can reduce risk.

TABLE 70-4

Agents Used to Treat Extrapyramidal Side Effects

Generic Name	Equivalent Dose (mg)	Daily Dosage Range (mg)
Antimuscarinics		
Benztropine[a]	1	1–8[b]
Biperiden[a]	2	2–8
Trihexyphenidyl	2	2–15
Antihistaminic		
Diphenhydramine[a]	50	50–400
Dopamine Agonist		
Amantadine	NA	100–400
Benzodiazepines		
Lorazepam[a]	NA	1–8
Diazepam	NA	2–20
Clonazepam	NA	2–8
β-Blockers		
Propranolol	NA	20–160

NA, not applicable.

[a]Injectable dosage form can be given intramuscularly for relief of acute dystonia.

[b]In treatment-refractory cases, dosage can be titrated to 12 mg/day with careful monitoring; nonlinear pharmacokinetics has been reported.

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Akathisia

- Akathisia affects 20%–40% of patients on high-potency FGAs, causing inner restlessness and/or physical symptoms such as pacing, shifting, shuffling, or tapping feet.
- Dose reduction is preferred when possible. Switching to an SGA may help; iloperidone, quetiapine, and clozapine have the lowest risk.
- Avoid benzodiazepines in those with a substance use history. **Propranolol** (up to 160 mg/day) is effective. 5-HT_2 antagonists such as **cyproheptadine**, **mirtazapine,** and **trazodone** may help prevent akathisia.

Parkinsonism

- The four cardinal symptoms are (1) akinesia/bradykinesia with reduced motor activity, such as mask-like facies and micrographia; (2) rest tremor, reduced by movement; (3) cogwheel rigidity, with jerky, ratchet-like limb movement; (4) stooped posture and slow, shuffling, or festinating gait.
- Accessory symptoms may include seborrhea, drooling, excessive sweating, fatigue, weakness, dysphagia, and dysarthria.
- Risk factors include high-dose FGA use, increasing age, and possibly being female.
- Symptoms begin 1–2 weeks after starting antipsychotics or increasing dose. SGA risk is low, except for risperidone over 6 mg/day. Quetiapine, aripiprazole, brexpiprazole, iloperidone, asenapine, lumateperone, and clozapine are good alternatives for EPS with other SGAs.
- **Benztropine** can be dosed once or twice daily, typically 1–2 mg twice daily, up to 8 mg/day. **Diphenhydramine** causes more sedation. All anticholinergics may be misused for their euphoriant effects (**Table 70-4**). **Amantadine** is as effective as anticholinergics with less impact on memory.
- Attempt to taper and discontinue these agents 6 weeks to 3 months after symptoms resolve.

Tardive Dyskinesia

- Tardive dyskinesia (TD) involves abnormal involuntary movements, typically shown as buccolingual-masticatory movements that affect chewing, speaking, and swallowing. TD may also include facial movements such as frequent blinking, brow arching, grimacing, upward deviation of the eyes, and lip smacking. Restless choreiform and athetotic movements of the limbs occur in later stages. These worsen with stress and lessen with sleep.
- Screen for TD at baseline using the Abnormal Involuntary Movement Scale (AIMS) and the Dyskinesia Identification System Condensed User Scale (DISCUS), repeating every 6 months for high-risk patients and annually for others.
- TD prevention strategies: (1) use SGAs as first-line treatment, (2) conduct biyearly TD screenings, and (3) discontinue or switch to SGAs at early TD symptoms, if possible.
- TD risk factors include long antipsychotic use, higher or cumulative dose, female sex, older age, acute extrapyramidal symptoms, poor response, organic mental disorders, diabetes, and mood disorders. TD prevalence with FGAs is 20%–50%; with SGAs, it's about 3% per year in younger adults versus 7.7% with FGAs.
- **Deutetrabenazine** and **valbenazine** VMAT2 inhibitors are approved for TD treatment in adults. They carry warnings for suicidality, depression, and QT prolongation.

OTHER ANTIPSYCHOTIC ADVERSE EFFECTS

Seizures

- Chlorpromazine and clozapine carry the highest risk, especially at treatment start, higher doses, or rapid increases.

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- Reduce dosage for an isolated seizure; antiseizure medication is usually unnecessary.
- If changing antipsychotics, consider aripiprazole, risperidone, thioridazine, haloperidol, pimozide, trifluoperazine, or fluphenazine.

Thermoregulation

- Poikilothermia, where body temperature adjusts to ambient temperature, is a serious antipsychotic side effect. Hyperpyrexia, risking heat stroke, can be dangerous in hot weather or during exercise. Hypothermia risk increases, especially in older adults.
- These issues are more common with low-potency FGAs and anticholinergic SGAs.

Neuroleptic Malignant Syndrome

- Neuroleptic malignant syndrome (NMS) occurs in <1% of patients, most commonly with high-potency FGAs.
- Symptoms appear within 24–72 hours: fever >38°C (100.4°F), altered consciousness, autonomic dysfunction (tachycardia, labile blood pressure, sweating, tachypnea), and rigidity.
- Common lab findings include myoglobinuria, leukocytosis, and elevated creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH).
- Discontinue antipsychotics and provide supportive care. Consider **dantrolene**, **bromocriptine**, or **amantadine** for severe cases.
- Antipsychotic rechallenge may be considered after 2 weeks off medication, using the lowest effective dose of an SGA, low-potency FGA, or XT, with careful monitoring and slow titration.

Endocrine Effects

- Elevated prolactin levels can cause galactorrhea, gynecomastia, decreased libido, and menstrual irregularities, common with FGAs, risperidone, and paliperidone. Consider switching to agents with lower risk such as aripiprazole, asenapine, iloperidone, lurasidone, brexpiprazole, lumateperone, or cariprazine. Avoid dopamine agonists due to the potential psychosis worsening.
- Antipsychotic weight gain is most likely with olanzapine, clozapine, risperidone, quetiapine, and iloperidone. Minimal weight gain is seen with ziprasidone, aripiprazole, lumateperone, lurasidone, brexpiprazole, and cariprazine.
- Patients with schizophrenia often have type 2 diabetes, worsened by antipsychotics. Olanzapine and clozapine have the highest risk for new-onset diabetes; followed by risperidone and quetiapine. Aripiprazole and ziprasidone likely present a lower risk. Asenapine, iloperidone, lurasidone, brexpiprazole, cariprazine, and lumateperone also appear to carry a lower risk, but more data are needed.
- Antipsychotic-induced weight gain may be polygenic and influenced by environmental factors.

Cardiovascular Effects

- Orthostatic hypotension (>20 mm Hg systolic drop) is most common with low-potency FGAs, clozapine, iloperidone, quetiapine, and combination antipsychotics. Older adults and those with diabetes or cardiovascular issues are more predisposed. Reducing the dose or switching to drugs with less α-adrenergic blockade may help, with tolerance possibly developing in 2–3 months.
- Thioridazine, clozapine, iloperidone, and ziprasidone are most likely to cause ECG changes such as increased heart rate, flattened T waves, ST depression, and QT/PR interval prolongation. Thioridazine extends QTc about 20 milliseconds more than haloperidol, risperidone, olanzapine, or quetiapine, with a dose-related effect and a boxed warning for torsades de pointes/sudden death.
- Iloperidone's pharmacogenomic metabolism increases QTc prolongation risk in CYP2D6 poor metabolizers. High IV haloperidol doses can also prolong QTc and carry a boxed warning.
- Discontinue medication if QTc consistently exceeds 500 milliseconds. Torsades is rare without risk factors such as age >60, female sex,

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cardiac/cerebrovascular disease, liver issues, low potassium/magnesium, other QTc-prolonging drugs, metabolic inhibition, or existing QTc prolongation.

- For patients over 50, pretreatment ECG and check serum potassium and magnesium levels.
- Myocarditis, though rare, is most associated with clozapine and has been reported with quetiapine and possibly olanzapine. Baseline and weekly monitoring of C-reactive protein (CRP) for 4 weeks is recommended, along with troponin (I or T) and B-type natriuretic peptide monitoring. Cardiomyopathy, a serious effect typically occurring 14 months into clozapine treatment, discourages rechallenges after myocarditis and is not advised after cardiomyopathy.
- Users of FGA and SGA have twice the risk of sudden cardiac death compared with nonusers, with the highest risk of ventricular arrhythmia or sudden death in the first few weeks of treatment.
- Individuals with schizophrenia on antipsychotics have a twofold higher risk of venous thromboembolism (VTE) than the general population. Proposed factors include sedative effects, metabolic changes, impact on platelet aggregation, and hyperprolactinemia increasing venous stasis.

Lipid Effects

- SGAs and phenothiazines can elevate triglycerides and cholesterol. Olanzapine, clozapine, and quetiapine have the highest dyslipidemia risk.
- Weight gain, diabetes, and lipid abnormalities during antipsychotic therapy are consistent with development of metabolic syndrome (consisting of raised triglycerides, ≥150 mg/dL [1.70 mmol/L]), low high-density lipoprotein cholesterol (≤40 mg/dL [1.03 mmol/L] for males, ≤50 mg/dL [1.29 mmol/L] for females), elevated fasting glucose (≥100 mg/dL [5.6 mmol/L]), blood pressure elevation (≥130/85 mm Hg), and weight gain (abdominal circumference >102 cm [40 in] for males, >89 cm [35 in] for females).

Psychiatric Effects

- Aripiprazole and brexpiprazole are linked to impulse control disorders like pathological gambling, uncontrolled sexual urges, spending, binge eating, and other intense urges.

Ophthalmologic Effects

- Antipsychotics and anticholinergics can worsen narrow-angle glaucoma.
- Chronic phenothiazine use, especially chlorpromazine, may cause corneal and lens deposits; periodic slit-lamp exams are advised.
- Quetiapine users should have baseline and periodic slit-lamp exams due to cataract risks seen in animal studies.
- Thioridazine doses over 800 mg daily can lead to retinitis pigmentosa and potential blindness.

Genitourinary System

- Urinary hesitancy and retention are common with low-potency FGAs, clozapine, and in males with benign prostatic hyperplasia.
- SGAs, especially clozapine, can cause urinary incontinence due to α-blockade.
- Risperidone and paliperidone cause similar sexual dysfunction as FGAs; other SGAs pose less risk.
- Priapism, a prolonged painful erection, is increasingly reported with antipsychotics.

Hematologic System

- Antipsychotics can cause transient leukopenia, typically not clinically significant. Clozapine, chlorpromazine, and olanzapine have the highest neutropenia risk.

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- Clozapine risk: 3% for neutropenia, 0.8% for agranulocytosis; higher risk with increased age and in females. The highest risk is between 1 month and 6 months of treatment. The initial ANC must be ≥1500/μL (1.5 × 109/L) to start clozapine. If ANC stays >1500/μL (1.5 × 109/L), monitoring decreases to biweekly for 6 months, then monthly. Discontinue clozapine and monitor daily if ANC drops <500/μL (0.5 × 109/L). Refer to product labeling for a detailed guidance on leukopenia monitoring.
- Agranulocytosis occurs in 0.01% of FGA patients, more often with chlorpromazine and thioridazine, typically within the first 8 weeks. Symptoms include sore throat, leukoplakia, erythema, and an ulcerated pharynx. Discontinue the antipsychotic and monitor closely for infection if there are symptoms and the ANC is <500/μL (0.5 × 109/L).

Dermatologic System

- Allergic reactions are rare, usually occurring within 8 weeks, and appear as maculopapular, erythematous, or pruritic rashes.
- Contact dermatitis may occur; swallowing FGA oral concentrates quickly may reduce oral mucosa rashes.
- Ziprasidone has a warning for the rare, potentially fatal Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) skin reaction.
- FGAs and SGAs can cause photosensitivity; patients should use strong sunscreens, hats, protective clothing, and sunglasses.
- Long-term, high doses of low-potency phenothiazines, such as chlorpromazine, may cause blue-gray skin discoloration and potential corneal or lens pigmentation.

Miscellaneous Adverse Effects

- Sialorrhea (drooling), often prominent at night, affects up to 54% of clozapine patients.
- Common XT adverse effects are nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness, and gastroesophageal reflux. Nausea or vomiting is the main reason for XT discontinuation.

USE IN PREGNANCY AND LACTATION

- Haloperidol is the best-studied FGA with about 400 reported exposures. A small study found a twofold increased risk of preterm birth in pregnant individuals with schizophrenia taking FGAs. In-utero FGA exposure raises the risk of neonatal EPS, with effects lasting 3–12 months post-birth.
- All SGAs cross the placenta. A meta-analysis noted increased risk of birth defects and preterm births with first-trimester SGA exposure, but no specific abnormalities were identified. Larger studies suggest aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone do not increase congenital or cardiac malformation risks. Large, well-controlled studies are needed for clearer safety data during pregnancy.
- FGAs have relative infant doses (RID) under 10%, generally considered safe. Olanzapine and quetiapine have RIDs under 4%, while risperidone and aripiprazole reach up to 9%. Clozapine use is not recommended while nursing due to the risk of severe neutropenia and seizures in the infant.

EVALUATION OF THERAPEUTIC OUTCOMES

- **Table 70-5** summarizes antipsychotic adverse effects, patient monitoring parameters, and frequency of monitoring parameters.
- The four-item Positive Symptom Rating Scale and the Brief Negative Symptom Assessment are useful in outpatient settings to track symptoms. Patient self-assessments engage them in treatment and aid education. Clinicians should aim for symptom remission assertively.

TABLE 70-5

Antipsychotic Adverse Effects and Monitoring Parameters

Adverse Reaction	Monitoring Parameter	Frequency	Comments

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Adverse Effect Monitoring Parameters for All Antipsychotic Medications			
Akathisia	Ask about restlessness or anxiety. Observe for restlessness. Use the Barnes Akathisia Scale to assess.	Every visit	
Anticholinergic adverse effects	Ask about constipation, blurry vision, urinary retention, or dry mouth.	Every visit	
Glucose intolerance	FBS or HbA1c	At baseline, after 3 months, and if normal, then annually	
Hyperlipidemia	Lipid profile	At baseline, after 3 months, and if normal, then annually	
Orthostatic hypotension	Ask about dizziness on standing. If present, check BP and HR in sitting and standing positions.	Every visit	Symptoms vary but a change of 20 mm Hg or more is generally significant.
Hyperprolactinemia	In females, ask about milk expression and menstrual irregularities. In males, ask about breast enlargement or milk expression. If symptoms occur, check serum prolactin levels.	Every visit	In the absence of symptoms, there is no need to monitor serum prolactin.
Sedation	Ask patient about unusual sedation or sleepiness	Every visit	
Sexual dysfunction	Ask patient about decreased sexual desire, difficulty being aroused, or problems with orgasm.	Every visit	Patients with schizophrenia experience more sexual dysfunction than the general population; compare symptoms with their medication-free state.
Tardive dyskinesia	Standardized rating scale such as the AIMS or the DISCUS	At baseline, and then every 6 months (FGAs) or 12 months (SGAs).	
Weight gain	Measure body weight, BMI, and waist circumference	BMI at baseline, then monthly for 6 months, and quarterly thereafter.	Waist circumference is the best predictor of cardiac morbidity.
Adverse Effect Monitoring Parameters for Specific Antipsychotics			
Agranulocytosis	ANC	At baseline, weekly for 6 months, then biweekly for 6 months, and finally monthly.	Clozapine only. REMS no longer required.
Sialorrhea or excess drooling	Ask the patient about excess drooling or waking with a wet pillow. Visually check for drooling.	Every visit	Clozapine only

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Gastrointestinal effects and hypertension	Ask about nausea, dyspepsia, constipation, vomiting, abdominal pain, diarrhea, dizziness, or gastroesophageal reflux. Monitor blood pressure.	Every visit	XT may have a higher incidence secondary to activity at muscarinic receptors
Bronchospasm, respiratory distress, respiratory depression, respiratory arrest	Before administration, screen patients for asthma, COPD, or other bronchospasm-related lung diseases. Monitor every 15 minutes for at least 1 hour after administration for bronchospasm signs (vital signs and chest auscultation). Only one 10-mg dose is allowed every 24 hours.	Every dose administration	Inhaled loxapine only. Can only be administered in approved healthcare facilities registered in REMS program.
Postinjection sedation/delirium syndrome	Observe the patient for at least 3 hours after administration. Monitor for sedation, altered consciousness, coma, delirium, confusion, disorientation, agitation, anxiety, or cognitive impairment.	Every dose administration	Olanzapine pamoate monohydrate is only administered in REMS-approved healthcare facilities.

AIMS, abnormal involuntary movement scale; ANC, absolute neutrophil counts; BMI, body mass index; BP, blood pressure; DISCUS, dyskinesia identification system condensed user scale; FBS, fasting blood sugar; FGA, first-generation antipsychotic; HbA1c, Hemoglobin A1c; HR, heart rate; REMS, Risk Evaluation and Mitigation Strategy; SGA, second-generation antipsychotic; XT, xanomeline/trospium.

See Chapter 91, Schizophrenia, authored by M. Lynn Crismon and Nina Vadiei, for a more detailed discussion of this topic.

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